THEMATIC REVIEW

Insulinomatosis: new aspects

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Abstract

Endogenous hyperinsulinemic hypoglycemia (EHH) is a rare condition with an incidence of approximately 4–6 per million person-years and comprises a group of disorders causing hyperinsulinemic hypoglycemia without exogenous administration of insulin or its secretagogues. In adults, most cases (approximately 90%) are secondary to a single insulinoma. Other causes include insulinoma in the context of multiple endocrine neoplasia type 1 (approximately 5% of cases) and non-insulinoma pancreatogenous hypoglycemia syndrome, which is estimated to account for 0.5–5% of all cases. Recently, an entity called insulinomatosis has been described as a novel cause of EHH in adults. The characteristic feature of insulinomatosis is the synchronous or metachronous occurrence of multiple pancreatic neuroendocrine tumors expressing exclusively insulin. While most cases arise sporadically, there is recent evidence that autosomal dominant inheritance of mutations in the v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog A (*MAFA*) gene can cause a familial form of insulinomatosis. In these families, EHH is paradoxically associated with the occurrence of diabetes mellitus within the same family. This review summarizes the current clinical, biochemical, imaging and genetic knowledge of this disease.

Key Words

- endogenous hyperinsulinemic hypoglycemia
- insulinomatosis
- MAFA gene

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Introduction

Endogenous hyperinsulinemic hypoglycemia (EHH) is a rare condition with an incidence of approximately 4–6 per million person-years (Grant 2005). A key diagnostic feature of EHH is the Whipple triad, which includes symptoms consistent with hypoglycemia, documentation of a low glucose concentration and relief of the symptoms after ingestion of carbohydrates (Cryer *et al.* 2009). Symptoms of hypoglycemia include those of the autonomous nerve system, such as sweating, weakness, tachycardia and hunger, as well as those of neuroglycopenia including a panoply of neurological symptoms including irritability, cognitive deficits and transient focal neurological deficits which may progress to seizures and coma (Valente *et al.* 2018). Thus, patients with EHH often present first to neurologists or even psychiatrists. An additional nonspecific, but helpful detail in the clinical history, is a significant increase in weight over recent years in more than 50% of patients (Jabri & Bayard 2004, Valente *et al.* 2018).

In adults, most cases (approximately 90%) of EHH are secondary to a single insulinoma, a well-differentiated insulin-producing pancreatic neuroendocrine tumor.

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In about 5% of cases, EHH is secondary to an insulinoma developing in the context of multiple endocrine neoplasia type 1 (MEN1; Anlauf *et al.* (2009)). A rare cause of EHH in adults is non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS) which is estimated to account for 0.5–5% of all EHH cases (Jabri & Bayard 2004). NIPHS represents a heterogenous group of disorders characterized by post-prandial hypoglycemia and beta cell hypertrophy (also known as nesidioblastosis) and includes both idiopathic forms and cases secondary to previous bariatric surgery (Klöppel *et al.* 2008). Recently, a novel cause of EHH in adults known as insulinomatosis has been described. Insulinomatosis is characterized by multiple insulinomas (predominantly micro-insulinomas) scattered throughout the entire pancreas in the absence of extra-pancreatic clinical manifestations. While the exact prevalence of insulinomatosis is unknown, in a large series of patients with adult-onset EHH, insulinomatosis accounted for 5% of all cases (Anlauf *et al.* 2009).

While insulinomas represent the most common cause of EHH in adults, most cases of EHH in children fall within the category of familial hyperinsulinism. This entity comprises cases with either congenital or childhood-onset hyperinsulinism and is secondary, in approximately 60% of probands, to pathogenic mutations in at least 14 different genes (Gillis 1993).

The differential diagnosis of EHH should include exogenous administration of insulin secretagogues or insulin (factitious hypoglycemia) as well as the insulin autoimmune syndrome (also known as Hirata's disease) (Service 1999). The clinical, biochemical and imaging characteristics of the different diagnoses are summarized in Table 1.

In a patient with symptoms consistent with hypoglycemia and documented hypoglycemia, additional biochemical assessment including insulin, C-peptide and, if possible, pro-insulin and beta-hydroxy-butyrate have to be performed in the emergency department or by performing a provocative test, the so-called prolonged fasting test (Cryer *et al.* 2009). This test consists of a maximum 72 h supervised fast in an inpatient setting with regular assessment of glucose, insulin and C-peptide levels and, in case of symptomatic hypoglycemia (usually neuroglycopenic symptoms), it is considered positive in the presence of inappropriate insulin and C-peptide levels with concomitant hypoglycemia. In case of suspicion of factitious hypoglycemia, assessment of oral hypoglycemic agents (sulfonylurea, meglitinides) and their metabolites is recommended (Cryer *et al.* 2009). In addition, the normal response of the counter-regulatory hormones should be documented, namely cortisol, growth hormone and glucagon (Cryer *et al.* 2009).

Morphological assessment in case of EHH

Once the biochemical diagnosis of EHH is established, morphological investigations are recommended (Falconi *et al.* 2016). Usually, conventional imaging is performed

Table 1 Differential diagnosis of endogenous hyperinsulinemic hypoglycemia (EHH) in adults.

Occurence of symptoms	Glucose (mmol/L)	C-peptide (nmol/L)	Insulin (pmol/L)	Additional parameters	Diagnosis
Fasting hypoglycemia	<3	>0.2	>20.8	Weight gain, single lesion on imaging. ^{68}Ga-Exendin-PET/CT pos	Insulinoma
Fasting hypoglycemia	<3	>0.2	>20.8	Weight gain, known MEN1 mutation and/or additional endocrine diseases like primary hyperparathyroidism and/or pituitary adenoma and/or adrenal adenomas. One or >1 lesions on imaging. ^{68}Ga-Exendin-PET/CT pos	Insulinoma(s) in the context of MEN1
Fasting or postprandial hypoglycemia	<3	>0.2	>20.8	Weight gain, no focal lesion on conventional imaging, focal or generalized increased uptake on molecular imaging possible. Often recurrent disease after surgery. Definitive diagnosis only on histology. Patients may have a history of bariatric surgery.	NIHPS
Fasting hypoglycemia	<3	>0.2	>20.8	Weight gain, one or >1 lesions on imaging. Often recurrent disease after surgery. Definitive diagnosis only on histology.	Insulinomatosis
Mainly postprandial	<3	>>0.2	>>20.8	Anti-insulin antibodies detectable. Negative imaging.	Insulin autoimmune syndrome
Mainly fasting	<3	>0.2	>20.8	Insulin secretagogues (sulfonylureas and meglitinides) detectable. Negative imaging.	Exogenous administration of oral hypoglycemic agents

MEN1, multiple endocrine neoplasia type 1; NIHPS, non-insulinoma pancreatogenous hypoglycemia syndrome.

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first, that is, contrast-enhanced magnetic resonance imaging (ceMRI) or contrast-enhanced computed tomography (ceCT) scan (Falconi *et al.* 2016). There is no clear evidence whether ceMRI outperforms ceCT (Falconi *et al.* 2016, Antwi *et al.* 2021). It is noteworthy that the inferior limit of detection of conventional imaging is approximately 0.5–1cm (Falconi *et al.* 2016, Antwi *et al.* 2021). If a lesion consistent with a neuroendocrine tumor is found on conventional imaging, surgery for insulinoma can be performed, including enucleation or more extensive surgery such as Whipple procedure or distal pancreatectomy depending on the size, location of the tumour and relationship to the pancreatic duct (Antwi *et al.* 2018, 2021). However, in approximately 20–30% of cases, the lesions cannot be localized and, in this case, additional investigations are recommended including endoscopic ultrasonography (EUS) or selective intra-arterial calcium stimulation with venous sampling (Falconi *et al.* 2016). Both are invasive procedures, whereas, in particular, the calcium stimulation test requires the selective cannulation of the different feeding arteries of the pancreas and the hepatic vein (Wiesli *et al.* 2004*a*). Although both tests have a high sensitivity and specificity, the EUS is operator-dependent and the results of the calcium stimulation test indicate only the arterial catchment area of the lesion and not the lesion itself (Falconi *et al.* 2016, Wiesli *et al.* 2004*b*). This is a drawback in the rare situation of ectopic insulinoma (Wild *et al.* 2008).

Molecular imaging is an elegant method to localize hidden pancreatic insulinomas. Insulin-secreting neuroendocrine tumors, including benign insulinomas as well as insulinomas in the context of MEN1 and probably insulinomatosis, do rarely overexpress somatostatin receptors subtype 2 (sst2) in contrast to other neuroendocrine tumors and, therefore, molecular imaging using ^{68}Ga-DOTATOC or DOTATATE is not always successful (Reubi 2003). However, ^{68}Ga-DOTATOC or DOTATATE PET/CT is meanwhile widely available and used for localizing insulin-secreting pancreatic neuroendocrine tumors with positive results in 50–60% of the cases (Falconi *et al.* 2016). In addition, there is evidence for a successful localization of the biggest lesion in a patient with possible insulinomatosis on histology using ^{68}Ga-DOTATATE PET/CT (Babic *et al.* 2016). Benign insulinomas overexpress GLP-1 receptors (Reubi 2003) and recent results of prospective trials indicate that the positron emitter ^{68}Ga linked to the GLP-1 analog exendin is a very sensitive method for non-invasive localization of insulinomas (Antwi *et al.* 2018). Personal experience indicates that the larger lesions in the case of insulinomatosis can also be visualized using this technique. However, lesions below the detection limit of PET imaging (<0.3–0.5 cm) cannot be identified. While imaging may allow the diagnosis of multifocal neuroendocrine tumors, it would not be possible to differentiate insulinomatosis from MEN1-related insulinomas on the basis of conventional or functional imaging. Family history, additional endocrine disorders (mainly primary hyperparathyroidism and pituitary tumors) and genetic testing can be helpful to diagnose EHH in the context of MEN1; however, for insulinomatosis, only the histological examination of the surgical sample will establish the diagnosis.

Clinical features of insulinomatosis

Approximately 22 cases of sporadic insulinomatosis and 3 kindreds with familial insulinomatosis have been described to date (Tragl & Mayr 1977, Anlauf *et al.* 2009, Iacovazzo *et al.* 2018, Snaith *et al.* 2020, Anoshkin *et al.* 2021, Mintziras *et al.* 2021, Fottner *et al.* 2022, Tartaglia *et al.* 2022). Among the patients with sporadic insulinomatosis, 17/22 are females (77.3%). All patients presented the first symptoms of the disease as adults, with a mean age at diagnosis of 42.6 years (range 17–64). The diagnosis was confirmed histologically in all cases. Overall, 11/22 patients had either persistent or recurrent EHH following the initial surgery and at least eight patients required more than one pancreatic resection. At the last follow-up, 16/22 patients were reported to be in clinical remission. It should be noted that, in two cases, insulin levels at the time of hypoglycemia were undetectable and the diagnosis was confirmed by measuring pro-insulin levels, which were inappropriately raised.

In the 3 families with familial insulinomatosis, 12 subjects were diagnosed with insulinomatosis (10 females; mean age at diagnosis 40.9 years, range 18–65). Eight patients underwent pancreatic surgery, and five required more than one operation. The remaining patients were managed with dietary changes and medical treatment with either diazoxide and/or somatostatin analogs. At the last follow-up, three out of eight patients who had undergone surgical treatment were reported to be in clinical remission. Importantly, at least 21 subjects in these families were diagnosed with diabetes mellitus (14 males; mean age at diagnosis for those with available data was 37.7 years, range 11–65). BMI was reported to be normal and there were no clinical features of insulin resistance in

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these patients. Hyperglycemia was mild to moderate and was managed with diet and/or oral hypoglycemic agents.

The clinical features of patients with available clinical and biochemical data are summarized in Table 2.

Histological features of insulinomatosis

The characteristic histological features of insulinomatosis are shown in Fig. 1 and consist of multiple insulin-expressing pancreatic neuroendocrine tumors, including predominantly micro-adenomas (<5 mm) and scattered macro-tumors (>5 mm), which develop both synchronously and metachronously (Anlauf *et al.* 2009). Over 100 micro-adenomas can be identified in patients with extensively sampled pancreatic resection specimens. The expression of insulin in all lesions discriminates insulinomatosis from other forms of micro-adenomatosis: in MEN1 patients, micro-adenomas express a range of different hormones, including predominantly glucagon and pancreatic polypeptide while in patients with Von Hippel-Lindau syndrome, micro-adenomas are typically negative for pancreatic hormones (Périgny *et al.* 2009). Glucagon-cell adenomatosis represents another condition of pancreatic micro-adenomatosis which can arise as a consequence of inactivating mutations in the glucagon receptor gene leading to glucagon resistance and hyperglucagonemia in the absence of glucagonoma syndrome (Zhou *et al.* 2009, Miller *et al.* 2015). While in glucagon cell adenomatosis the multiple glucagon-producing micro-adenomas are accompanied by islet cell hyperplasia, hyperplastic islets are not a feature of insulinomatosis. Furthermore, insulinomatosis differs from nesidioblastosis, as the latter is a non-neoplastic condition characterized by islets with hypertrophic beta cells without tumor formation (Klöppel *et al.* 2008). Interestingly, no cases of lymph node or distant metastases have been reported to date in patients with insulinomatosis, while MEN1-related pancreatic neuroendocrine tumors have the potential for metastatic spread which occurs in approximately 20–30% of patients.

Genetic background of insulinomatosis

While most patients with insulinomatosis present with sporadic disease, rare instances of familial insulinomatosis with autosomal dominant inheritance patterns have been described. Recently, two different missense mutations in the *MAFA* gene have been identified in three unrelated families: Ser64Phe (Iacovazzo *et al.* 2018) and Thr57Arg (Fottner *et al.* 2022). MAFA belongs to the family of large MAF transcription factors and is expressed in islet β cells. It is required for postnatal β cell function and acts as a transactivator of insulin and several genes involved in glucose-stimulated insulin secretion (Zhang *et al.* 2005, Artner *et al.* 2010).

Both missense mutations (Ser64Phe and Thr57Arg) resulted in the development of an adult-onset dual phenotype of either insulinomatosis (more likely in female carriers) and interestingly also MODY-like diabetes mellitus (more likely in male carriers) (Iacovazzo *et al.* 2018, Fottner *et al.* 2022). Four cases of congenital eye disease (including glaucoma and/or congenital cataracts) were reported in one family, including two homozygous mutation carriers (Iacovazzo *et al.* 2018). The disease presents with high penetrance (Iacovazzo *et al.* 2018, Fottner *et al.* 2022). Importantly, both mutations are located in highly conserved residues within the transactivation domain (Iacovazzo *et al.* 2018, Fottner *et al.* 2022). Functionally, the Ser64Phe mutation impairs the phosphorylation cascade of MAFA with impairment of transactivation activity and degradation (Iacovazzo *et al.* 2018). The Thr57Arg mutation is expected to have a similar effect on MAFA phosphorylation since it affects one of the residues which are phosphorylated by GSK3 and are relevant in determining the stability and transactivation activity of MAFA (Benkhelifa *et al.* 2001, Guo *et al.* 2009).

The two phenotypes of *MAFA* mutations, namely insulinomatosis and MODY-like diabetes mellitus, possibly dependent on gender, are intriguing and the underlying mechanisms remain to be established. Interestingly, the same Ser64Phe mutation causes diabetes mellitus selectively in male mice, while female carriers are hypoglycemic with improved glucose clearance (Walker *et al.* 2021). The potential effects of sex hormones were investigated in this animal model: ovariectomy at three weeks resulted in glucose intolerance in wildtype mice by four weeks of age, while glucose sensitivity was unaffected in mutant mice, suggesting that the effect of the S64F mutation was dominant over the effects of estrogen deficiency. Furthermore, testosterone levels in four- and five-week-old male mice were expectedly low and similar to those observed in age-matched females, suggesting that the effects of androgens on the development of the sexual dimorphic phenotype would be negligible and that the diabetic phenotype might precede the onset of puberty in males. Overall, these data suggest that additional

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Table 2 Clinical features of the published patients with insulinomatosis with available clinical and biochemical data.

ID	Sex	Age at diagnosis	Biochemistry at diagnosis (fasting test)	Treatment	TNM staging (UICC 8th edition)	Tumor grading	Persistent or recurrent disease after initial surgery	References
Fa1 III/1	M	30	Glu 2.1, Ins 316.7, C-pep 1.7	Enucleation ×2, diazoxide + verapamil	pT1(m) N0	G1	Yes	Iacovazzo *et al.* (2018)
Fa1 III/8	F	48	Glu 2.6, Ins 319.4, C-pep 0.3	Octreotide + verapamil + dexamethasone	n/a	n/a	n/a	Iacovazzo *et al.* (2018)
Fa1 III/11	F	44	Glu 2.5, Ins 77.8	Partial pancreatectomy, octreotide + diazoxide	pT1(m) N0	G1	Yes	Iacovazzo *et al.* (2018)
Fa1 III/12	F	53	Glu 2.3, Ins 84, C-pep 0.8	Verapamil	n/a	n/a	n/a	Iacovazzo *et al.* (2018)
Fa1 III/19	F	48	Glu 2.7, Ins 105.7	Partial pancreatectomy ×2, total pancreatectomy	pT1(m)	G1	Yes	Iacovazzo *et al.* (2018)
Fa1 IV/4	F	18	Glu 2.8, Ins 125, C-pep 0.7	Partial pancreatectomy, octreotide + verapamil + dexamethasone	n/a	n/a	Yes	Iacovazzo *et al.* (2018)
Fa2 II/1	M	38	Glu 0.9, Ins 1389 (after glucagon)	Enucleation, partial pancreatectomy, diazoxide	n/a	n/a	Yes	Tragl & Mayr (1977), Iacovazzo *et al.* (2018)
Fa2 III/1	F	28	Glu <1.1, Ins 1111.2 (after tolbutamide)	Enucleation, partial pancreatectomy, diazoxide, partial pancreatectomy, completion total pancreatectomy	n/a	G1	Yes	Tragl & Mayr (1977), Iacovazzo *et al.* (2018)
Fa2 III/3	F	65	Glu 2.4, Ins 18.8	Diazoxide	n/a	n/a	n/a	Tragl & Mayr (1977), Iacovazzo *et al.* (2018)
Fa3 IV/4	F	38	Glu 0.9, Ins n/a, C-pep n/a	Partial pancreatectomy ×2	pT1(m) N0	G1	Yes	Fottner *et al.* (2022)
Fa3 IV/3	F	53	Glu 1.9, Ins 97.2, C-pep 1	Partial pancreatectomy	pT1(m) N0	G1	No	Fottner *et al.* (2022)
Sp1	F	17	Glu 1.9, Ins 104, C-pep 1	Enucleation ×2, diazoxide + dexamethasone, Whipple	pT1(m) N0	G1	Yes	Iacovazzo *et al.* (2018)
Sp2	F	48	Glu 2.3, Ins 137.5, C-pep 0.8	Diazoxide + prednisone, partial pancreatectomy, diazoxide, octreotide	pT1(m) N0	G1	Yes	Iacovazzo *et al.* (2018)
Sp3	F	64	Ins undetectable, pro-Ins 20.4, C-pep 0.1 (in the presence of hypoglycemia)	Partial pancreatectomy ×2	pT1(m) N0	G1	Yes	Iacovazzo *et al.* (2018)
Sp4	F	47	Glu 1.8, Ins 27.8, pro-Ins 41, C-pep 0.6	Distal pancreatectomy	pT1(m) N0	G1	No	Iacovazzo *et al.* (2018)
Sp5	F	51	Glu 1.59, Ins 37.5, pro-Ins 29.4, C-pep 0.2	Distal pancreatectomy	pT1(m) N0	G1	No	Iacovazzo *et al.* (2018)
Sp6	F	40	Glu 1.6, Ins 305.6, pro-Ins 122, C-pep 1.8	Enucleation ×2, total pancreatectomy, diazoxide, everolimus	pT2(m) N0	G2	Yes	Snaith *et al.* (2020)
Sp7	F	48	Glu 2, Ins 13.9, pro-Ins 12.1, C-pep 0.08	Enucleation, distal pancreatectomy	pT2(m) N0	G1	Yes	Mintziras *et al.* (2021)
Sp8	F	41	Glu 2.4, Ins 25.7, C-pep 0.4	Distal pancreatectomy, octreotide	pT1(m) N0	G1	Yes	Tartaglia *et al.* (2022)

C-pep, C-peptide (nmol/L); F, female; Fa, familiar case; Glu, glucose (mmol/L); Ins, insulin (pmol/L); M, male, n/a, not available/applicable; pro-ins, pro-insulin (pmol/L); Sp, sporadic case.

genetic or environmental factors other than exposure to sex hormones are implicated in the sexual dimorphism observed in *MAFA* mutation carriers.

While all described instances of familial insulinomatosis are a consequence of an *MAFA* mutation, the genetic background of sporadic insulinomatosis, which comprises the majority of reported cases of the disease, is still unknown. An in-frame single histidine deletion in the *MAFA* gene has been reported in a patient with sporadic insulinomatosis (Mintziras *et al.* 2021). However, this appears to represent a common polymorphism as deletions or duplications involving the

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histidine repeats in this region of the gene are extremely common in the general population. Next-generation sequencing of a panel of cancer-related genes in a case of sporadic insulinomatosis highlighted the presence of somatic copy number variants affecting several tested genes, including *FOXL2*, *IRS2*, *CEBPA* and *ATRX* (Anoshkin *et al.* 2021). It is, however, uncertain how these would contribute to the pathogenesis of the disease.

Treatment of insulinomatosis

Due to the multicentric nature of the disease, treatment of EHH in the context of insulinomatosis is challenging. In the original case series, six out of 14 patients (43%) had persistent or recurrent disease following surgical treatment (either enucleation, distal pancreatectomy or Whipple procedure) (Anlauf *et al.* 2009). It should be noted, however, that some patients achieved disease remission following either initial or repeat surgery (typically distal pancreatectomy). In the two families carrying the Ser64Phe *MAFA* mutation, six patients underwent surgery, with persistent or recurrent EHH in all cases (Iacovazzo *et al.* 2018). Four of the six patients required more than one operation, including two subjects who developed insulin-dependent diabetes mellitus following the completion of total pancreatectomy. In the third family, two patients were diagnosed with insulinomatosis, including one patient with persistent EHH following distal pancreatectomy who eventually required a new surgical resection to achieve disease remission (Fottner *et al.* 2022). One case of sporadic insulinomatosis with persistent EHH despite total pancreatectomy has been recently described, suggesting the presence of microscopic remnants of pancreatic tissue causing persistent hyperinsulinism (Snaith *et al.* 2020). Responsiveness to medical treatment, including diazoxide or somatostatin analogs, is largely anecdotal

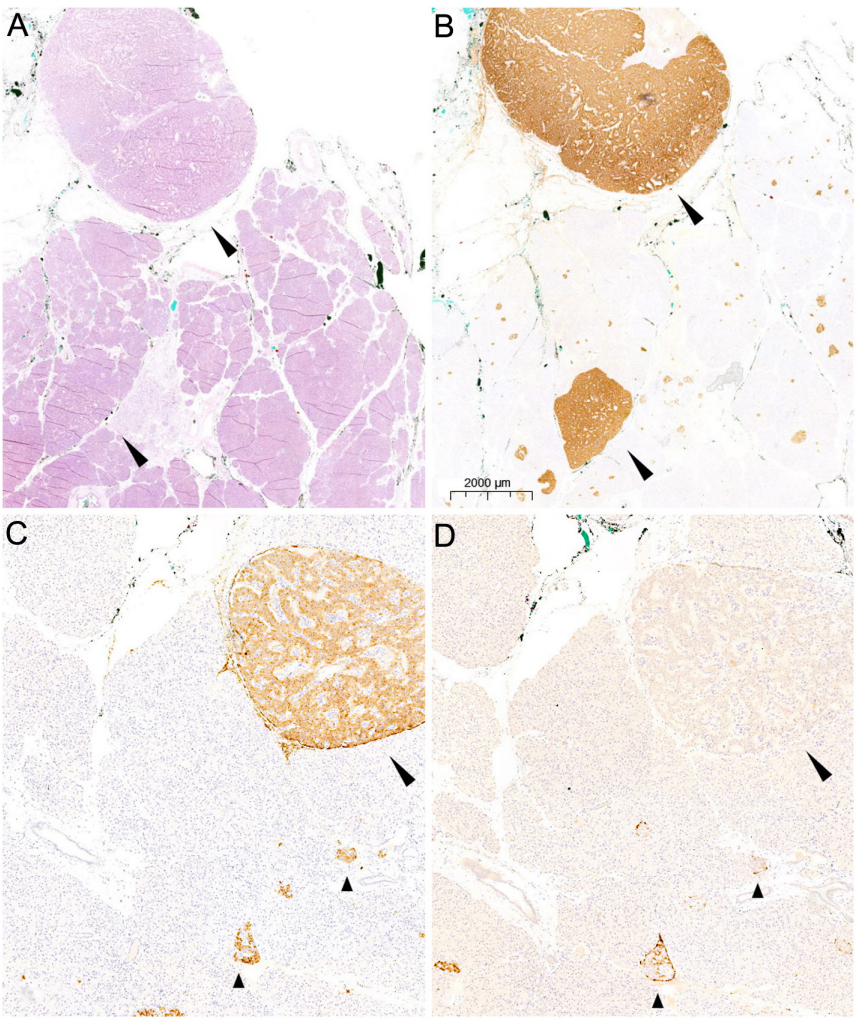

Figure 1
Histopathology of sporadic insulinomatosis. (A) HE, 50× and (B) Insulin staining, 50×: Two insulin producing micro-tumors, staining for insulin.(C) Third micro-tumor staining for insulin, below normal islets. (D) Glucagon staining negative in the micro-tumor, but positive in normal α-cells at the periphery of normal islets. Long arrowheads, neuroendocrine tumors; short arrowheads, normal islets.

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considering the rarity of the disease. Poor results with persistent hypoglycemia were reported in patients with familial insulinomatosis (Iacovazzo *et al.* 2018). However, a case of complete remission of an insulinoma has been recently described in a patient with sporadic insulinomatosis following treatment with octreotide long-acting release (Tartaglia *et al.* 2022). Dietary changes with frequent consumption of complex carbohydrates have been shown, in our experience, to help alleviate the symptoms of hypoglycemia in patients with persistent episodes of hypoglycemia.

Conclusion

EHH is a rare and heterogeneous clinical entity. Insulinomatosis is a recently described cause of EHH in adults and is characterized by the occurrence of multiple insulinomas scattered throughout the pancreas. While most patients present with sporadic disease, in some cases, the disease can present in a familial setting with an autosomal dominant inheritance pattern. In these families, insulinomatosis occurs more frequently in female carriers while male carriers develop MODY-like diabetes mellitus with high penetrance. This dual phenotype has been recently shown to result from missense mutations in the *MAFA* gene, encoding a key β cell transcription factor, while the genetic background of sporadic insulinomatosis is still largely unknown. Clinically, biochemically and with regard to localization using conventional or molecular imaging, insulinomatosis cannot be differentiated from single insulinomas or other rare causes of EHH, including insulinoma in the context of MEN-1 or NIPHS. Only the histological assessment by an experienced pathologist can establish the diagnosis.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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References

Anlauf M, Bauersfeld J, Raffel A, Koch CA, Henopp T, Alkatout I, Schmitt A, Weber A, Kruse ML, Braunstein S, *et al.* 2009 Insulinomatosis: a multicentric insulinoma disease that frequently causes early recurrent hyperinsulinemic hypoglycemia. *American Journal of Surgical Pathology* **33** 339–346. (https://doi.org/10.1097/PAS.0b013e3181874eca)

Anoshkin K, Vasilyev I, Karandasheva K, Shugay M, Kudryavtseva V, Egorov A, Gurevich L, Mironova A, Serikov A, Kutsev S, *et al.* 2021 New regions with molecular alterations in a rare case of insulinomatosis: case report with literature review. *Frontiers in Endocrinology* **12** 760154. (https://doi.org/10.3389/FENDO.2021.760154)

Antwi K, Fani M, Heye T, Nicolas G, Rottenburger C, Kaul F, Merkle E, Zech CJ, Boll D, Vogt DR, *et al.* 2018Comparison of glucagon-like peptide-1 receptor (GLP-1R) PET/CT, SPECT/CT and 3T MRI for the localisation of occult insulinomas: evaluation of diagnostic accuracy in a prospective crossover imaging study. *European Journal of Nuclear Medicine and Molecular Imaging* **45** 2318–2327. (https://doi.org/10.1007/S00259-018-4101-5)

Antwi K, Wiesner P, Merkle EM, Zech CJ, Boll DT, Wild D, Christ E & Heye T 2021 Investigating difficult to detect pancreatic lesions: characterization of benign pancreatic islet cell tumors using multiparametric pancreatic 3-T MRI. *PLoS One* **16** e0253078. (https://doi.org/10.1371/journal.pone.0253078)

Artner I, Hang Y, Mazur M, Yamamoto T, Guo M, Lindner J, Magnuson MA & Stein R 2010 MafA and MafB regulate genes critical to β-cells in a unique temporal manner. *Diabetes* **59** 2530–2539. (https://doi.org/10.2337/db10-0190)

Babic B, Keutgen X, Nockel P, Miettinen M, Millo C, Herscovitch P, Patel D, Nilubol N, Cochran C, Gorden P, *et al.* 2016 Insulinoma due to multiple pancreatic microadenoma localized by multimodal imaging. *Journal of Clinical Endocrinology & Metabolism* **101** 3559–3563. (https://doi.org/10.1210/jc.2016-2717)

Benkhelifa S, Provot S, Nabais E, Eychène A, Calothy G & Felder-Schmittbuhl MP 2001 Phosphorylation of MafA is essential for its transcriptional and biological properties. *Molecular and Cellular Biology* **21** 4441–4452. (https://doi.org/10.1128/MCB.21.14.4441-4452.2001)

Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ & Endocrine Society 2009 Evaluation and management of adult hypoglycemic disorders: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* **94** 709–728. (https://doi.org/10.1210/JC.2008-1410)

Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, Kos-Kudla B, Kwekkeboom D, Rindi G, Klöppel G, *et al.* 2016 ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. *Neuroendocrinology* **103** 153–171. (https://doi.org/10.1159/000443171)

Fottner C, Sollfrank S, Ghiasi M, Adenaeuer A, Musholt T, Schad A, Miederer M, Schadmand-Fischer S, Weber MM, Lackner KJ, *et al.* 2022 Second MAFA variant causing a phosphorylation defect in the transactivation domain and familial insulinomatosis. *Cancers* **14**. (https://doi.org/10.3390/CANCERS14071798)

Gillis D 1993 Familial hyperinsulinism. *GeneReviews®*.

Grant CS 2005 Insulinoma. *Best Practice and Research. Clinical Gastroenterology* **19** 783–798. (https://doi.org/10.1016/j.bpg.2005.05.008)

Guo S, Burnette R, Zhao L, Vanderford NL, Poitout V, Hagman DK, Henderson E, Özcan S, Wadzinski BE & Stein R 2009 The stability and transactivation potential of the mammalian MafA transcription factor are regulated by serine 65 phosphorylation. *Journal of Biological Chemistry* **284** 759–765. (https://doi.org/10.1074/jbc.M806314200)

Iacovazzo D, Flanagan SE, Walker E, Quezado R, De Sousa Barros FA, Caswell R, Johnson MB, Wakeling M, Brändle M, Guo M, *et al.* 2018 MAFA missense mutation causes familial insulinomatosis and diabetes mellitus. *PNAS* **115** 1027–1032. (https://doi.org/10.1073/pnas.1712262115)

Jabri AL & Bayard C 2004 Nesidioblastosis associated with hyperinsulinemic hypoglycemia in adults: review of the literature. *European Journal of Internal Medicine* **15** 407–410. (https://doi.org/10.1016/J.EJIM.2004.06.012)

Klöppel G, Anlauf M, Raffel A, Perren A & Knoefel WT 2008 Adult diffuse nesidioblastosis: genetically or environmentally induced? *Human Pathology* **39** 3–8. (https://doi.org/10.1016/J.HUMPATH.2007.09.010)

Miller HC, Kidd M, Modlin IM, Cohen P, Dina R, Drymousis P, Vlavianos P, Klöppel G & Frilling A 2015 Glucagon receptor gene mutations with hyperglucagonemia but without the glucagonoma syndrome. *World Journal of Gastrointestinal Surgery* **7** 60–66. (https://doi.org/10.4240/WJGS.V7.I4.60)

Mintziras I, Peer K, Goerlach J, Goebel JN, Ramaswamy A, Slater EP, Kann PH & Bartsch DK 2021 Adult Proinsulinomatosis associated with a MAFA germline mutation as a rare cause of recurrent hypoglycemia. *Pancreas* **50** 1450–1453. (https://doi.org/10.1097/MPA.0000000000001933)

Périgny M, Hammel P, Corcos O, Larochelle O, Giraud S, Richard S, Sauvanet A, Belghiti J, Ruszniewski P, Bedossa P, *et al.* 2009 Pancreatic endocrine microadenomatosis in patients with von Hippel-Lindau disease: characterization by VHL/HIF pathway proteins expression. *American Journal of Surgical Pathology* **33** 739–748. (https://doi.org/10.1097/PAS.0b013e3181967992)

Reubi JC 2003 Peptide receptors as molecular targets for cancer diagnosis and therapy. *Endocrine Reviews* **24** 389–427. (https://doi.org/10.1210/er.2002-0007)

Service FJ 1999 Classification of hypoglycemic disorders. *Endocrinology and Metabolism Clinics of North America* **28** 501–517. (https://doi.org/10.1016/S0889-8529(05)70085-2)

Snaith JR, McLeod D, Richardson A & Chipps D 2020 Multifocal insulinoma secondary to insulinomatosis: persistent hypoglycaemia despite total pancreatectomy. *Endocrinology, Diabetes and Metabolism Case Reports* **2020** 20-0091. (https://doi.org/10.1530/EDM-20-0091)

Tartaglia A, Busonero G, Gagliardi L, Boddi V, Pieri F & Nizzoli M 2022 Complete remission of recurrent multiple insulin-producing neuroendocrine tumors of the pancreas with somatostatin analogs: a case report and literature review. *Discover. Oncology* **13** 66. (https://doi.org/10.1007/S12672-022-00531-Z)

Tragl KH & Mayr WR 1977 Familial islet-cell adenomatosis. *Lancet* **2** 426–428. (https://doi.org/10.1016/S0140-6736(77)90609-2)

Valente LG, Antwi K, Nicolas GP, Wild D & Christ E 2018 Clinical presentation of 54 patients with endogenous hyperinsulinaemic hypoglycaemia: a neurological chameleon (observational study). *Swiss Medical Weekly* **148** w14682. (https://doi.org/10.4414/SMW.2018.14682)

Walker EM, Cha J, Tong X, Guo M, Liu JH, Yu S, Iacovazzo D, Mauvais-Jarvis F, Flanagan SE, Korbonits M, *et al.* 2021 Sex-biased islet β cell dysfunction is caused by the MODY MAFA S64F variant by inducing premature aging and senescence in males. *Cell Reports* **37** 109813. (https://doi.org/10.1016/J.CELREP.2021.109813)

Wiesli P, Brändle M, Schmid C, Krähenbühl L, Furrer J, Keller U, Spinas GA & Pfammatter T 2004a Selective arterial calcium stimulation and hepatic venous sampling in the evaluation of hyperinsulinemic hypoglycemia: potential and limitations. *Journal of Vascular and Interventional Radiology* **15** 1251–1256. (https://doi.org/10.1097/01.RVI.0000140638.55375.1E)

Wild D, Mäcke H, Christ E, Gloor B & Reubi JC 2008 Glucagon-like peptide 1–receptor scans to localize occult insulinomas. *New England Journal of Medicine* **359** 766–768. (https://doi.org/10.1056/NEJMc0802045)

Zhang C, Moriguchi T, Kajihara M, Esaki R, Harada A, Shimohata H, Oishi H, Hamada M, Morito N, Hasegawa K, *et al.* 2005 MafA is a key regulator of glucose-stimulated insulin secretion. *Molecular and Cellular Biology* **25** 4969–4976. (https://doi.org/10.1128/MCB.25.12.4969-4976.2005)

Zhou C, Dhall D, Nissen NN, Chen CR & Yu R 2009 Homozygous P86S mutation of the human glucagon receptor is associated with hyperglucagonemia, alpha cell hyperplasia, and islet cell tumor. *Pancreas* **38** 941–946. (https://doi.org/10.1097/MPA.0b013e3181b2bb03)

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